A Better Understanding of BPA Metabolism, with Frederick vom Saal

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Bisphenol A (BPA) is used in a wide variety of consumer products, and biomonitoring studies indicate widespread exposure to the compound. Much of the hesitation to regulate BPA up to now has stemmed from uncertainty about whether health effects reported in laboratory animals-which include heart disease, obesity, diabetes, reproductive health problems, and several types of cancer—can be extrapolated to humans. In this podcast, Frederick vom Saal discusses recent findings that suggest mice, rhesus monkeys, and humans metabolize BPA at similar rates, raising the possibility that effects observed in animal models may be relevant to humans as well. Vom Saal is a Curator's Professor of biology at the University of Missouri.

AHEARN: It's The Researcher's Perspective. I'm Ashley Ahearn.

Bisphenol A, or BPA, is used in a wide variety of consumer products, from the liners of canned goods to the receipts printed from the register at the grocery store. Worldwide, an estimated 8 billion plus pounds of BPA are produced each year.[1]

Over 90% of the U.S. population is estimated to have BPA in their bodies, according to the Centers for Disease Control and Prevention. And more and more research has raised concerns about potential health effects of BPA, linking it with heart disease, obesity, diabetes, reproductive health problems, and several types of cancer.

But the majority of this research was conducted on animals, not people—and that raises questions about whether the same effects apply to humans.

In a new study Dr. Fred vom Saal set out to explore the similarities between mice, monkeys, and people when it comes to metabolizing BPA, and what those similarities could mean for human health. He's a Curator's Professor of biology at the University of Missouri, and his research was recently published online in EHP.[2]

Hi, Dr. vom Saal.

VOM SAAL: Hello, Ashley. Thanks for having me on the program.

AHEARN: So, why don't you start by telling me how your study was conducted and what were you hoping to figure out.

VOM SAAL: We compared the ability of mice to metabolize bisphenol A at exactly the same dose given to rhesus monkeys, which, in terms of their metabolism of chemicals such as BPA, are thought to be very good models or surrogates for estimating effects in humans. We then compared our mouse and monkey data with previously published data from humans, and so we were able to get a very good look at the question of whether mice and monkeys and humans really differ in the way they handle BPA.

AHEARN: And what did you find?

VOM SAAL: Well, the most important finding here is that when looked at at the same administered dose,[3] you get the same rate of clearance in the mouse, the rhesus monkey, and the human. And in a way this is kind of surprising because the mouse is a very small animal and rhesus monkeys weigh about 15, 16 pounds, and humans, you know, 150. And yet when you administer them bisphenol A, the blood levels generated are very similar, and the rate of clearance is very similar.

AHEARN: Much of the hesitation to regulate BPA up to now has stemmed from uncertainty about whether results seen in lab animals can actually be applied to humans, and it seems like your research is directly addressing that problem. What does this mean?

VOM SAAL: Well, in terms of the handling of BPA from the point of view of metabolism—how fast is it taken up, and how fast is it removed—the mice and rat studies are relevant to humans, and that's important because we know the cellular responses and the organ responses in animals and humans are virtually identical.

AHEARN: Your paper discusses "conjugated" versus "unconjugated" or "free" BPA. What do those terms mean, and why is that distinction important?

VOM SAAL: Well, one of the things that we have shown was false about the statements being made about BPA is in industry reviews of BPA they've said virtually all bisphenol A, greater than 99%, would be metabolized in the liver after being ingested, and it would be converted to an inactive or conjugated form of bisphenol A that was unable to act as a sex hormone.[4,5] And one of the things we showed is that that estimate of virtually complete metabolism is absolutely not true in mice and monkeys and is therefore very likely to not be true for humans.

AHEARN: So we're actually measuring the wrong form of BPA.

VOM SAAL: Up until now the only data from humans was the metabolized form of BPA, and that isn't going to tell you how much of the hormonally active form of BPA is present. In our experiment we did both: we looked at the biologically active form and the metabolized form, and there is a lot more free bisphenol A present after administration than anybody had been predicting. Our data show very convincingly that we are already exposed to at least eight times higher levels of BPA than the current and outdated safe level.[6]

AHEARN: Dr. vom Saal, when you look at people around you and you see these kinds of epidemic health problems in the population, do you scratch your head and think, "Hmm, could this be related to our widespread exposure to BPA?" and what kind of problems do you see that may be linked, in your mind?

VOM SAAL: Well, if you look at the major public health issues and health trends over the last 30, 40 years, subsequent to the chemical revolution that occurred after World War II, you look at diseases such as diabetes and obesity and heart disease that, clumped together, are called metabolic disease, and all of these diseases are increasing. And

bisphenol A in animal studies causes these diseases. And in fact, using the national health survey [the National Health and Nutrition Examination Survey], heart disease, type 2 diabetes, and obesity are in fact related to blood levels of bisphenol A in the U.S. population.[7] So, this is of tremendous concern.

The other thing is that developmental exposure to bisphenol A at very low amounts below, clearly, what we are being exposed to, predisposes animals to prostate cancer[8] and breast cancer.[9,10,11]

And then finally, the reproductive system, of course—this is a sex hormone. In males it reduces sperm production,[12] and in females, interestingly, it's related to miscarriage, uterine fibroids, and polycystic ovaries, and it causes early puberty.[13]

AHEARN: Dr. vom Saal, what changes are you seeing in public awareness of BPA, and what do you see happening next in terms of regulation?

VOM SAAL: Well, I think one of the things that's clearly happening is that 10 years ago if you were to tell somebody about BPA, they would say, "I've never heard of this." I think the great majority of Americans now are beginning to recognize that there are chemicals in products that they don't want to be exposed to themselves and in particular they don't want their babies and children to be exposed to. So, this is clearly driving state legislators to make decisions, and there's no doubt that the regulatory system is going to have to respond to the public pressure that's occurring now and move on BPA. And in fact, at the beginning of 2010, the FDA [U.S. Food and Drug Administration] did something that it doesn't do very often, and that is, it reversed its position and basically said that it was going from stating that bisphenol A was completely safe to having concern about BPA.[14] And there's a big initiative by the National Institute of Health to look at the health consequences of BPA,[15] and the FDA has said it will use this information to change its position, if warranted by the data, in terms of trying to regulate this chemical.[13]

AHEARN: Dr. vom Saal, thanks so much for joining me.

VOM SAAL: Been a pleasure.

AHEARN: Dr. Fred vom Saal is a Curator's Professor of biology at the University of Missouri.

And that's The Researcher's Perspective. I'm Ashley Ahearn. Thanks for downloading!

References and Notes

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[3] Dose is adjusted for body weight.

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[6] According to Taylor et al. (2010), the high end of the range of median values reported for unconjugated BPA in human serum corresponded to the highest levels the authors observed in rhesus females after oral administration of 400 µg/kg/day BPA. The current U.S. Environmental Protection Agency oral reference dose (or maximum acceptable intake) for BPA is 50 µg/kg/day.

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[11] Durando M, et al. Prenatal bisphenol A exposure induces preneoplastic lesions in the mammary gland in Wistar rats. Environ Health Perspect 115(1):80–86 (2007); doi:10.1289/ehp.9282.
[12] Impaired sperm production has been observed in numerous animal studies but has not been confirmed in men. However, some studies have reported associations between BPA exposure and reduced sperm quality in humans [e.g., Meeker JD, et al. Semen quality and sperm DNA damage in relation to urinary bisphenol A among men from an infertility clinic. Reprod Toxicol 30(4):532–539 (2010); doi:10.1016/j.reprotox.2010.07.005].
[13] Studies have revealed evidence of effects of BPA exposure during development on the reproductive tract of female mice, including cystic ovaries [Newbold RR, et al. Prenatal exposure to environmentally relevant doses adversely affects the murine reproductive tract later in life. Environ Health Perspect 117(6):879–885 (2009); doi:10.1289/ehp.0800045] and, in a small number of cases, leiomyomas (a.k.a. fibroids) [Newbold RR, et al. Long-term adverse effects of neonatal exposure to bisphenol A on the murine female reproductive tract. Reprod Toxicol 24(2):253–258 (2007) doi:10.1016/j.reprotox.2007.07.006]. Evidence of effects in humans is far rarer. One recent cross-sectional study reported an association between serum BPA and polycystic ovary syndrome (PCOS) in 71 women compared with 100 women without PCOS [Kandaraki E, et al. Endocrine disruptors and polycystic ovary syndrome (PCOS): elevated serum levels of bisphenol A in women with PCOS. J Clin Endocrinol Metab; doi:10.1210/jc.2010-1658 (online 30 Dec 2010)], and a cross-sectional study reported an association between serum BPA levels in 45 women with a history of three or more first-trimester miscarriages compared with 32 women without a history of miscarriages, but not with future miscarriages [Sugiura-Ogasawara M, et al. Exposure to bisphenol A is associated with recurrent miscarriage. Hum Reprod 20(8):2325–2329 (2005); doi:10.1093/humrep/deh888].
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